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Influenza and the work of the World Health Organization

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Abstract

Before World War I, influenza was not considered a particularly serious problem. The great pandemic of 1918–1919 changed all that, and the possibility that such a catastrophe could occur again has conditioned all subsequent developments.

In epidemiological terms, the hallmark of an influenza is the excess mortality that it causes combined with an enormous burden of ill-health that saps the energy of individuals, families and communities throughout the whole world. In order to engage in influenza prevention and control, the global influenza surveillance network was set up by World Health Organization (WHO) in 1948 as a worldwide alert system for the identification of new influenza viruses, gathering information from 110 participating laboratories in 82 countries and four WHO Collaborating Centers for Influenza reference and research: Centers for Disease Control and Prevention, Atlanta (USA), National Institute for Medical Research, London (UK), WHO Collaborating Centre for Influenza Reference and Research, Melbourne (Australia) and the National Institute for Infectious Diseases, Tokyo (Japan).

This network helps WHO to monitor influenza activity all over the world and provides the organization with the viral isolates and information it requires to decide which new virus strains will be used to produce influenza vaccines during the following season. Each year, information about the isolates over the previous 12 months is analyzed and used to determine the composition of the influenza vaccine to be administered during the coming influenza season both for the northern and southern hemisphere. If necessary, the recommendations for the southern hemisphere differ from the ones formulated for the northern hemisphere vaccine. The information supplied by this network enables the organization to regularly update its World Wide Web (WWW) site (FluNet), which reports on the situation of diseases.

This network will also enable the WHO to detect a new influenza pandemic as early as possible.

Keywords: Influenza; Surveillance; Prevention; Control; Epidemic; Pandemic; FluNet; Human; Animal; Vaccine

1. Introduction

Before World War I, health care officials did not think that influenza was a particularly serious problem. In contrast to the major scourges of the past century (smallpox, typhus, cholera and the like), no one was concerned about influenza epidemics. When influenza caused deaths, mortality was confined largely to infants, the elderly and the weak.

The great influenza pandemic of 1918–1919 changed perceptions about influenza. In only a few months, influenza caused probably the worst plague in history. It is estimated that the pandemic killed tens of millions of people, with some estimates totaling upwards towards 40 million deaths, and infected half of the world's population. This pandemic had unprecedented virulence. Furthermore, unlike previous outbreaks, the pandemic was particularly fatal to young adults. This pandemic stimulated many countries to develop public health programmes against influenza. The possibility that a similar catastrophe could occur again has influenced all subsequent developments in influenza programmes.

The major characteristic of an influenza pandemic is that it causes "excess mortality". Additionally, the pandemic places an enormous burden of ill-health on public health that saps the energy of individuals, families and communities throughout the entire world.

In 1946, the Interim Commission (IC) of the World Health Organization (WHO) was established to develop the initial programme of WHO. In 1948, the Interim Commission organized and financed the World Influenza Center at the National Institute for Medical Research in London, which was the first international influenza center. This step marked the beginning of the WHO influenza programme [1]. At that time, the programme was primarily a "research project" to study the epidemiology of influenza [2].

In 1950, The Third World Health Assembly emphasized the importance of influenza and approved the proposal to convene an Expert Committee on Influenza. The first meeting of the Expert Committee on Influenza took place in September 1952. Before the meeting, committee members reviewed the information obtained on influenza during

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previous years. At the meeting, the committee members planned for more effective international cooperation on influenza [3].

The Expert Committee envisaged that, by cooperating with an international network of laboratories, WHO could advise member states regarding control of influenza. WHO would also coordinate surveillance on the appearance and spread of influenza in order to accurately forecast the time and place of influenza epidemics. Furthermore, WHO felt that antigenic studies of prevalent viruses would permit the committee to recommend the strains of viruses that should be included in the influenza vaccine and to recommend which vaccines in stock could be used.

2. Influenza epidemiology

2.1. Influenza viruses

Before the viral nature of human influenza was demonstrated in the early 1930s, scientists thought that a bacteria caused influenza. This belief arose from studies conducted by the German bacteriologist Richard Pfeiffer, immediately following the 1889–1890 epidemic. Despite conflicting evidence, Pfeiffer, himself, was not yet ready in 1930 to believe that his bacillus did not cause influenza [4]. In 1933, Andrewes et al. [5] and Laidlaw [6] initiated a series of experiments that proved conclusively that influenza had a viral nature.

It soon became clear that the virus described by Smith and his colleagues did not account for all influenza cases. It was not until 1940, however, when Francis isolated another virus, similar to the first but antigenically quite distinct, that a more complete picture of the family of influenza viruses emerged. Then, the earlier virus was named influenza virus A and the virus of Francis was named influenza virus B [7].

A third form, C, was discovered in 1951. Influenza A is responsible for major epidemics and pandemics and influenza A is the only form that is found both in animals and in humans. The outbreaks of B tend to be smaller and less severe than those of A. Influenza C does not cause epidemics and causes only mild infections.

From the moment that strain differences among influenza A viruses were first recognized in 1938, scientists documented that the influenza A virus was not stable and continuously changed genetically. In contrast, other viruses, such as polio virus or measles virus, remain stable.

As the subtypes of the influenza virus are better understood, it has been necessary on several occasions to revise the system of nomenclature for these viruses. The WHO Expert Committee in 1952 adopted a standard naming system which consisted of four parts: the virus type (A, B, or C); the location where the virus was first recovered; the serial number, to designate which of several strains isolated at the same place is referred to; and the year of isolation. Thus a new strain might be called A/England/1/53 [1]. As further subtypes were identified, in 1959, the WHO Expert Committee on Respiratory Virus Diseases made provision for their identification, e.g. A_2/Singapore/1/57. This rather simple scheme did not permit the separate recognition of both H and N antigens. When it was learned that these antigens undergo independent antigenic variation, in 1972, the system was revised to include these antigenic variations [8]. All previous A subtypes were reclassified and grouped according to both the H and N antigen.

During a meeting in 1980 in Geneva, there was another change of designation of animal and human influenza A virus subgroups [9]. The H antigens were divided into 12 subtypes and the N antigens were divided into nine subtypes. For example, Shope's swine flu was combined with closely related H and N subtypes and classified as H1N1.

Since the 1980 meeting, the number of N antigens has remained the same while an additional three H antigens have been discovered. Thus, today there are 15 known influenza A hemagglutinin (H) and nine neuraminidase (N) types. While humans have become infected with non-human influenza viruses, as witnessed by the recent type A(H5N1) and A(H9N2) cases in Hong Kong, only three H (H1, H2 and H3) and two N (N1 and N2) subtypes have been successfully established in man.

2.2. Global influenza surveillance

The influenza surveillance programme was organized in 1948. WHO is one partner in the global effort and wants to strengthen and expand the influenza surveillance system (FluNet). FluNet is a major component in a worldwide alert system designed to monitor emerging diseases. It is planned that this global surveillance/alert system (FluNet) will cover the entire world and will cooperate with specialised laboratories and national surveillance systems. With the rapid growth of electronic transmission of information to all corners of the globe, FluNet will become even more important in the future.

The influenza surveillance network of WHO identifies new influenza viruses by obtaining information from 110 participating laboratories in 82 countries and four WHO Collaborating Centers for Influenza reference and research: Centers for Disease Control and Prevention, Atlanta (USA), National Institute for Medical Research, London (UK), WHO Collaborating Center for Influenza Reference and Research, Melbourne (Australia) and the National Institute for Infectious Diseases, Tokyo (Japan). Each year, researchers must constantly investigate and classify the new circulating influenza viruses in order to prepare an effective vaccine. To do this, National Influenza Centers and the four WHO Collaborating Centers are continuously and systematically exchanging isolated influenza viral strains.

This network helps WHO to monitor influenza activity in many countries of the world and provides the viral isolates and information required to decide which new virus strains will be used to produce influenza vaccines during the following influenza season. Each year, the network analyzes

information about the isolates over the previous 12 months and recommends the composition of the influenza vaccine for the coming influenza season either for the northern or the southern hemisphere. WHO wants to strengthen its network of national centers and is encouraging all governments to give the resources required to facilitate the exchange of information and reagents between centers, to increase the number of centers in developing countries and to ensure that all centers are linked electronically and are in regular contact. The influenza network regularly supplies information to WHO and to FluNet, which is the World Wide Web (WWW) site that contains information about the current influenza situation.

2.3. Pandemic influenza

Epidemics of influenza have been identified as far back in history as the 12th century. Since the 15th century, 45 serious epidemics of influenza have been documented [10]. Many epidemics were named after their presumed origin (Russian catarrh, Chinese flu, Scottish rant). Many 18th and 19th century writers did not think that influenza could spread from one geographic area to another. Some people believed that influenza was a contagious infection. However, the more prevalent belief was that atmospheric poisons or miasma, meteorological phenomena, and telluric factors such as volcanoes or earthquakes caused and/or spread influenza [11].

The first time that maps were used to illustrate the spread of the infection was during the great pandemic of 1889–1890 [11]. Pandemics are world wide disease outbreaks. Influenza pandemics result from the emergence of an influenza A virus that is novel for humans and that is sufficiently virulent to cause severe infection. After approximately 50 years without pandemics, there was the influenza pandemic of 1889–1890. Ten years later, there was the influenza pandemic of 1899–1900. The great influenza pandemic occurred in 1918 and was followed by pandemics in 1957–1958 and 1968–1969. Both pandemics of the late nineteenth century spread across oceans within several months. The great epidemic of 1918 coincided with the last phase of World War I, during which time, waves of military and civil populations moved across continents, thus, ensuring that the virus infected almost all corners of the globe.

More recent pandemics have moved even more quickly due to the speed of modern transportation and the urbanization of an expanding human population [12]. The following incident demonstrates the speed and efficiency of spread of influenza. In 1977, a plane with 54 passengers, of whom one had influenza, was repaired. During repairs, the plane's air conditioning system was turned off for 3 h. Soon, 72% of the passengers came down with a genetically identical influenza [13].

The constant epidemic threat from the influenza virus is largely due to the rapid rate of mutation and evolution in nature. When the virus changes, there is the distinct possibility that a new strain will emerge and humans will not be immune to this new strain. Continuous mutation is common with RNA viruses. In the process of reproduction, RNA material must unwind, divide and reconstitute itself. Genetic "proof-reading" or verification, present in micro-organisms containing a DNA genome, is lacking. When two different A viruses infect the same cell, extraneous pieces of RNA from one virus may be copied onto the other virus, yielding an intact parent virus with slightly different offspring. Even small errors are encoded permanently in the new progeny of the virus.

"Antigenic drift" are minor antigenic changes. Such genetic mutation is due to selective pressure on the virus from the large population of partially immune people, who have antibodies to the virus because of previous infections [14]. This process is continuous and causes local epidemics of influenza. Major antigenic changes ("antigenic shift") are much less frequent and are due to a radical change to either the H or N surface protein. Where the new virus is so completely different that few people are immune to it, a pandemic of life-threatening infections may result. Scientists should study the pandemics of 1957 and 1968 so that they can better understand the dynamic nature of influenza in the world.

The pandemic of 1957 began with the appearance of A(H2N2) viruses in the Far East. The prototype strain was designated as A/Japan/302/57(H2N2) and is commonly called the Asian influenza virus. At that time, the appearance of this different A subtype was the "most abrupt shift in the recorded history of influenza viruses" [3].This virus was first isolated in the Yunan province in China in February 1957 and then in Hong Kong in April 1957. The virus quickly spread to Singapore, Taiwan and Japan. The path of its progress was studied by laboratories all over the world, largely because of the distinctive antigen of the virus. The virus apparently reached the outside world by two routes: along the Trans-Siberian Railway into the (then) USSR and by sea from Hong Kong to Singapore and Japan [15,16].

Asian influenza reached the USA soon thereafter, seeding the population during the summer and becoming epidemic as soon as schools were back in session in September [12]. The seasonal pattern of excess mortality was similar to the excess mortality observed during the great pandemic of 1918. The A(H2N2) virus remained prevalent in the USA population for 10 years. During this time, new variants (antigenic drifts) emerged to produce major epidemics in early 1963 and in the winter of 1967–1968.

In 1957, Asian influenza lasted 6–8 weeks in Melbourne. Some 45% of the population had been infected as judged by a rise of antibody titer. On the average (mathematically determined), each infected individual transferred the virus to 1.2 persons. When the increasing percentage of immune individuals reached a sufficiently high level, the rate of spread was not enough to maintain the epidemic and it terminated [17].

The 1968 pandemic, due to an H3N2 virus, became known as A/Hong Kong influenza. Only the hemagglutinin (H) surface glycoprotein had changed (antigenic shift); the

N2 neuraminidase had been present in the previous H2N2 pandemic. H2N2 viruses disappeared from human circulation when the H3N2 virus emerged, just as the H1N1 virus had ceased to circulate in 1957 when the H2N2 strain appeared.

The spread of the 1968 virus was at first very similar to that of the 1957 virus, with epidemics in Singapore and other southeast Asian countries [12]. However, it proved to be less severe than the earlier Asian pandemic. However, it is still causing disease for reasons that are not well understood [12]. It is believed that decreased severity was due to a cross immunity resulting from the fact that the N2 neuraminidase was common to the virus of the preceding pandemic. Antibodies to the influenza neuraminidase (N) do not prevent infection but may modify the extent of infection by reducing the amount of virus released during each replication. In the US, another important factor was the timing of the epidemic. In the US, schools closed for the Christmas holidays just as the epidemic was gaining momentum, which may have slowed the subsequent progress of the first epidemic wave [12].

Serological studies suggest that the H protein of the virus of the 1957–1958 pandemic (H2) was similar to the H protein of the influenza virus that caused the 1889–1890 pandemic. The H protein of the virus that caused the pandemic of 1968–1969 (H3) was similar to the H protein of the virus of the 1899–1900 pandemic. The WHO Influenza Center in the Netherlands discovered in June 1957 that antibodies of the then spreading Asian flu (H2N2) were present in some persons over 70 years of age [2]. WHO was informed and the collection of sera from elderly persons in other areas was quickly organized. These confirmed that the Asian flu was identical or similar to the pandemic of 1889–1890, a result that may not have been evaluated had the new epidemic reached these areas before the collection of sera was completed.

Further confirmation that the pandemics of the last century were caused by A virus subtypes that have reappeared was obtained in the late 1970s when samples collected before the H3N2 pandemic in 1968 from people born before 1887 contained antibodies to H3-like agents. Given that the 1889–1890 pandemic had been determined to be of a H2N2 class, this result suggested that the later pandemic, i.e. that of 1899–1900, was due to H3N2-like viruses [18].

The great pandemic of 1918 has been caused by a type A(H1N1) virus, i.e. one that was different from earlier pandemics in both H as well as N surface glycoproteins. Suggested by earlier serological studies, this has been confirmed recently, when the examination of autopsy specimens taken from a soldier known to have died from influenza in 1918 proved to be the H1N1 type [19]. The ability of an “old” virus to re-emerge was again demonstrated with the reappearance in 1977 of the influenza A(H1N1) virus, whose prototype was first seen in the USSR. It was identical to a virus that circulated in the USA in 1950 [12].

2.4. Link with animals and birds

Early literature noted concurrent epidemics among humans and animals. Horses were named most of the time but dogs and cats were also occasionally mentioned. Later other domestic and wild animals were added to this list, in particular pigs and ducks. The 1889–1890 epidemic coincided with an apparent equine influenza outbreak leading many to speculate that there was a relationship between the two. Also of interest is the fact that Iowa farmers believed that the disease they called hog flu (Shope’s swine flu) was first seen in October 1918 when that great epidemic reached US, arguing that the swine had contracted the human disease [17]. There is still no consensus concerning which flu preceded the other.

Given the long history of suspected human-animal flu interaction, it is not surprising that WHO’s influenza programme has been actively tracking both human and animal strains over the last half century. Working from the hypothesis that human epidemics and pandemics may arise from an animal reservoir, it was learned during the 1957 pandemic that human influenza could cause natural asymptomatic infection in swine. Also, avian influenza can affect a large variety of domestic and migratory avian species including chickens, ducks, turkeys, quails, pheasants and terns. The isolation in both Scotland and the Republic of South Africa of almost identical strains from wild tern, a species that migrates great distances, indicates that avian influenza strains must be widely circulating throughout the world [17]. Subsequent studies have revealed hitherto unsuspected connections between equine, avian and human strains [20].

Comparison of the 1957 pandemic H2 virus with the H3 form of the Hong Kong flu showed that the amino acid sequences of both differed greatly. Since laboratory experiments had demonstrated the emergence of antigenic hybrids from mixing infection of pigs, turkeys, and chickens and it had been found that the frequency of recombinant viruses from mixed infections is very high, it was hypothesized in 1972 that the 1968 Hong Kong virus (H3N2) had not arisen by mutation from a pre-existing human strain but, instead, had evolved through genetic recombination involving an animal or bird with an animal or avian influenza virus and a human A/Asian strain [21]. Subsequently, it was shown that the human H3N2 subtype evolved as a result of genetic recombination between a human H2N2 virus and an influenza A virus from an unidentified species. It had acquired seven of the eight genes from the H2N2 virus and one gene, which coded for the H antigen, from the other virus [9].

In 1968, it was unsuspected that influenza viruses from animals and birds are involved in the origin of pandemic strains of influenza A. However, over the past two decades, this fact has become progressively accepted [16]. It would now appear that aquatic birds, particularly ducks, are the primary host of influenza A viruses, since aquatic birds contain all of the 15 hemagglutinin and nine neuraminidase subtypes [16].

Another aspect of the animal link is the belief that pigs, infected by both an avian and human influenza virus, serve

as the host of a process (mixing vessel) which leads to an exchange of genetic material, potentially resulting in more virulent forms of the virus [14]. There have been many instances where humans have become infected by influenza viruses originating in pigs. However, to date, only the H1 and H3 subtypes have been found in pigs [16].

There is even the possibility that humans may be an alternate "mixing vessel"! Results from studies conducted on sera from various regions in China show considerable evidence of human responses to a range of subtypes of influenza. The presence of an antibody response implies some replication of the virus in humans, even though this may be limited and inadequate for further transmission. As most of these subtypes have yet to be detected in the pig, it seems probable that birds are infecting humans directly, implying that there would be an opportunity for reassortment to occur directly in humans with existing human strains [16]. This has been further substantiated by the recent H5N1 and H9N2 infections in humans in Hong Kong [22–25].

From these and other facts, three theories concerning the emergence of pandemic viruses have been put forward:

1. Genetic reassortment occurring in man or between human and animal viruses;
2. Direct transfer of viruses between animals and humans;
3. Re-emergence of viruses from unrecognised or unsuspected reservoirs.

The first theory is based on the fact that both of the 1957 and 1968 pandemic viruses contained genes derived from avian influenza viruses and human viruses. Currently, it is believed that both pandemics originated in southern China, where ducks and pigs are in close contact with humans,. Thus, it is possible that the pig was an "intermediate host". Agriculture in parts of Asia, uses fresh manure from livestock, particularly ducks and pigs, for fishponds. In Malaysia, for example, duck faeces are eaten by pigs, which in turn defecate into ponds used for fish culture. This biologically rich situation probably greatly enhances genetic reassortments of many kinds.

The second theory is based on genetic studies indicating that the 1918 H1N1 pandemic virus originally came from an avian source [26]. Viruses with avian genetic characteristics have also been recovered from horses and aquatic mammals [12]. Genetic study of the H1N1 descendants of the 1918 virus isolated during the 1930s suggests that this virus was not formed by reassortment but by adaptation of an avian virus to humans. It has been suggested that this process may have occurred following adaptation in the pig as an intermediary. Nevertheless, there is as yet little direct evidence of avian viruses infecting humans [16].

Superimposed on both the reassortant and direct transfer theories, is the possibility that only certain H subtypes (i.e. H1, H2, H3) have epidemic potential in humans as shown by the re-emergence of these subtypes over the past century. Such a theory is based on studies of antibodies in sera from people alive during earlier pandemic periods. This serologic data suggests that the pandemic virus in 1889 had an H2 haemagglutinin, related to that found in the 1957 pandemic virus, and that the pandemic virus in 1900 had an H3 haemagglutinin related to that found in the 1968 pandemic virus. Similarly, the type A(H1N1) virus, which reappeared in 1977, had both haemagglutinin and neuraminidase genes (as well as all other genes) essentially the same as found in H1N1 virus from 1950. If this theory of limitation on the sub-types capable of infecting and transmitting in man is true, it is not known whether these subtypes can be maintained for 20–80 years between pandemics only in the form of animal influenza viruses or are maintained in some other way. It is certainly difficult to explain the close overall similarity between the 1977 and 1950 type A(H1N1) viruses without invoking "dormancy", which therefore should be considered, in theory, as a third possible mechanism for emergence of pandemic influenza viruses, despite the lack of knowledge of how influenza virus could remain hidden for many years.

However, it must not be forgotten that there is the possibility that a major antigenic drift may cause a pandemic, such as occurred at a limited level in 1947 with the A(H1N1) strains [27].

3. Prevention and control of influenza

3.1. Vaccination

By the end of the last century, it was realized that resistance to certain communicable diseases could be produced by injection of their germs in an attenuated live state, or by inoculation with extracts from such organisms when dead [28]. Following Pasteur's vaccine against rabies, one after another disease has had some form of vaccine developed, with varying degrees of success. During the great influenza pandemic of 1918, various flu vaccines were developed. In the state of Illinois alone, 18 different kinds of vaccines were tried. Although lacking any immunologic value, these had a great deal of prestige, and for a while, it was believed that they helped provide some protection [29].

It was only after the 1933 discovery of the influenza virus that valid immunization results began to emerge, slowly at first, but steadily thereafter. An important first step was the demonstration, in 1937, by Macfarlane Burnet that influenza virus that had been passed many times through chicken embryos was nonpathogenic for ferrets and mice but was immunogenic and conferred protection against challenge with virulent virus [30].

Because the 1918 pandemic had a disastrous impact on the military, the development of an influenza vaccine was given immediate priority at the onset of World War II. Burnet, working with the Australian army, concentrated on the development of a live vaccine, while the USA military favored an inactivated vaccine. By 1943 results in USA were sufficiently encouraging to dissuade further live vaccine

development at that time. Methods for large-scale production of killed vaccine were soon developed. In 1942, the US Armed Forces Commission on Influenza established a central reference laboratory to study and compare strains of virus isolated in different places.

Vaccines stimulate the production of antibodies, which can attach to the surface H and N antigens and thus, reduce the replication capabilities of the virus. Antibodies are specific to the antigens used in the vaccine; i.e. vaccines can only provide protection against viruses with identical or very similar antigens as were used to construct the vaccine. Even antibodies acquired naturally from previous exposure to flu viruses do not offer permanent protection. For reasons not fully understood, the quantity of antibodies decreases in time.

Extensive experience with vaccines has demonstrated that vaccines can give a high degree of protection. While results vary from trial to trial, typical rates of protection are from about 70% to more than 90% in healthy immunocompetent individuals. Influenza vaccine reduces the risk of mortality and serious illness. It also can contribute to the creation of herd immunity in a community, i.e. achieving a level of immunity sufficiently high to measurably reduce attack rates in the community [31]. However, if the vaccine administered provides less than 70% protection, the vaccine will not stop the epidemic.

In 1947, the need to update the vaccine according to the virus type in circulation was demonstrated. An experimental vaccine, which had given good results in the 1943–1944 outbreak, did not give any protection in 1947 [2]. Whereas earlier, protection rates of 70–90% had been achieved, the 1934 and 1943 components of the vaccine did not give more than 9% protection in 1947 [32]. The virus concerned throughout this period was a type A(H1N1), but the virus causing the 1947 epidemic had evolved though antigenic drift and differed considerably from that of earlier strains.

It was important for vaccine research to continue in light of many factors discussed by the 1st WHO Expert Committee in 1952 [1]. These included: how to determine the optimal mix of strains to include in a vaccine; assessing the value and safety of vaccine containing adjuvants to enhance the antigenic immunogenicity; what vaccination methods to use to avoid adverse reactions; how to test the potency of influenza virus vaccines; and how to plan and assess field trials.

On the practical side, there has always been the problem of the time required to implement full scale production [1]. One constraint in this regard was the impossibility to prepare “storage supplies” on a mass scale since the antigenic drift inevitably leads to a mismatch with newly circulating influenza viral strains.

Determining the optimal vaccine composition of strains to be incorporated has proved to be a problem in influenza control. On one hand, it would be desirable to have as many strains as possible to provide the most protection. On the other hand, to be effective, an adequate mass of viral antigen must be given. In 1966 it was recommended that not more than two strains of virus A and two of virus B should be included in the vaccine [33]. One alternative, current then, was the use of a composite vaccine containing strains involved in former epidemics and pandemics. Some vaccines included as many as seven strains [34].

The viruses judged most likely to pose epidemic threats are candidates for the next cycle of vaccine production. Time may be short between the recognition of the emergence of a new pandemic virus and the occurrence of the first wave. The lead-time for the production and distribution of the currently licensed influenza vaccine is 6 months [12].

Since 1973, WHO has organized a meeting in February each year to agree upon the vaccine strains to be used for the production of the new vaccine. Representatives of the four WHO Collaborating Centers for Reference and Research on Influenza and the US FDA, the Australian TGA, and British NIBSC attend this meeting. Two A strains plus one B strain are chosen for inclusion in the vaccine for the forthcoming year. For example, the following trivalent vaccine was recommended by WHO for the 2000–2001 northern hemisphere influenza season:

- A/Moscow/10/99 (H3N2)-like strain;
- A/New Caledonia/20/99 (H1N1)-like strain; and
- B/Beijing/184/93-like strain.

Since 1998, in September, WHO has made formal recommendations for influenza vaccine composition for the southern hemisphere. If necessary, the recommendations for the southern hemisphere differ from the ones formulated for the northern hemisphere vaccine.

- In 2000, the formulation recommended for the 2000 Australian winter, was the same as the one mentioned above for the northern hemisphere, but may differ (and has in the past) according to influenza strains circulating in the southern hemisphere.

The ideal time for vaccination varies because of the differing epidemiology of influenza in different geographic regions. In the northern hemisphere, it is September–October. In temperate southern hemisphere regions it is usually accepted that vaccination should take place in March–April. However, later vaccination may still be effective because the peak period for outbreaks is most commonly June–September. In tropical and sub-tropical areas influenza activity tends to have less distinct peak seasons and may occur throughout much of the year, but often with two periods in which increased activity occurs. Based on rather limited data it appears that in the southern hemisphere tropical/sub-tropical regions the first peak is often around February–March with a second around September–October.

3.2. Other measures

When the first Influenza Expert Committee met in 1950 it identified a series of measures for combating epidemics of influenza which included quarantine, restriction of

movement of individuals, avoidance of crowds in cinemas, public meetings, etc., and the provision of extended hospital services.

The 1918 experience no doubt contributed to the 1952 Expert Committee concluding, that the responsibility for mortality in influenza epidemics probably depends in part upon the character of the virus. The exact measure of success to be expected with antibacterial agents in a virulent pandemic is therefore to some extent unpredictable [1].

The tendency for the 1957 pandemic to first appear in camps, army units, schools and other communities where contact between individuals was particularly close, suggested that avoidance of crowding may be important in reducing the peak incidence of an epidemic [1]. Other measures, such as wearing masks, adequate ventilation and disinfection of the air in selected buildings, were considered to have doubtful value [1].

The first Expert Committee on Respiratory Virus Diseases, in 1958, agreed with the 1950 recommendations, while adding some points learned from the 1957 pandemic. First, there was clear indication that quarantine measures resulted at best, in providing a short delay in the onset of the epidemic. Israel provided the most striking example of the possibilities of quarantine. Israel had been cut off from its neighboring states and experienced the 1957 pandemic about 2 months after its neighboring states. For quarantine to be effective, it must be very severe—so severe as to seriously interfere with international travel and trade.

The 1958 Expert Committee concluded that the coverage of the world by the WHO network should be made more complete, and its operation made speedier and more efficient. Diagnostic methods should be made simpler and more reliable. Vaccines need to be improved, and new or more effective means of treatment and control should be sought. Today most of these recommendations remain valid.

Diagnostic methods used today are mainly those that were used at the time the WHO global programme was initiated. These include: the hemagglutination-inhibition test for antigenic analysis of isolates; embryonated eggs to grow reference antigens; and infection of ferrets to raise polyclonal reference sera [16]. However, improved culture systems for isolating influenza viruses have been developed, along with the use of direct antigen detection methods. What is still needed is a sensitive, rapid, reliable, and inexpensive direct antigen detection method that could identify an influenza A virus and differentiate H1, H3 and non-H1–H3 subtypes [16].

Recent progress on treatment has been made. The desired features of antiviral substances were outlined by the WHO Scientific Group that met in 1967 [34] and recommended that such substances to be clinically useful should prevent infection, stop viral growth, or eliminate the virus from the cell. Failing this, they ought to suppress virus multiplication sufficiently to permit an effective host mechanism to control the infection.

Since the vast majority of influenza deaths occur from secondary bacterial infection of the lung, treatment of these infections with antibiotics is an essential feature of any control programme. Evidence pointing to the possible participation of bacteria not only as opportunistic invaders of virus-damage bronchioles, but as enhancers of virus virulence by facilitating hemagglutinin cleavage, increases the importance of rapid and adequate treatment of bacterial infection [32]. The 1918 pandemic was particularly fatal due to the viral pneumonia present, one that was particularly deadly among the strongest and healthiest youth that became infected [32]. A similar clinical outcome with extensive tissue damage in several organs, probably related to direct virus induced pathogenic effects, was observed during the “chicken flu” H5N1 episode in Hong Kong in 1997.

By 1979, amantadine, an antiviral drug useful for influenza control, had been developed. It was highly effective prophylactically against influenza A only, reducing the incidence of disease by as much as one-half [35]. Later, rimantadine, which is chemically related to amantadine, was developed. When administered prophylactically to healthy adults or children before and throughout the epidemic period, both antiviral drugs are approximately 70–90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses [36]. Also, both drugs can reduce the severity and duration of signs and symptoms of influenza A illness when administered within 48 h of illness onset.

Zanamivir and oseltamivir, two new antiviral drugs which inhibit neuraminidase in influenza virus types A and B, have been licensed [37,38]. Although these are the first drugs recognized to be effective against influenza B, their application is still limited since they must be administered within 48 h (alike for amantadine/rimantadine), a time lag difficult to respect under normal clinical conditions.

3.3. Pandemic surveillance

Information from historical records, sero-archeology, and molecular epidemiology indicates that there will definitely be another influenza pandemic among humans [39]. Or, as Kennedy Shortridge has put it, “each year brings us closer to the next pandemic” [40]. Predicting when the next pandemic will strike is impossible, as vividly demonstrated by the lack of an epidemic in the USA in 1976.

The viruses that caused the 1918 pandemic and the viruses that provided gene segments for the Asian/57 and Hong Kong/68 pandemics are still circulating in wild birds, with few or no mutational changes. If recycling occurs, as suggested in the history of pandemics over the last century, then the next human pandemic is likely to be caused by the H2 subtype, since it has been nearly 30 years since this subtype last infected humans [39]. Not only is there now a susceptible population to support a pandemic by these viruses, H2N2 viruses have been isolated from birds in live-poultry

markets in the USA, where susceptible individuals could have direct contact with such viruses.

While scientists continue to struggle with understanding the origin of "likely" candidates for the next pandemic, it is in the field where candidates are selected. It is critical that early warning be obtained of any new strain found in circulation. In both 1957 and 1969, it was 6 weeks after the first outbreaks outside of China when the new pandemic strains were identified and made available to vaccine manufactures [41]. Much time could have been gained if this identification been made when the first signs of an epidemic were observed. In 1957, after satisfying its own essential needs, almost no country could manufacture in time significant quantities of vaccine for export [3].

Reacting to the 1957 pandemic, the 1958 Expert Committee stressed that the WHO programme should now be regarded as an essential part of the world-wide public health defense against influenza, and the laboratory network, originally organized under the programme, should be brought into closer relationship with national public health authorities [3]. In this way national centers could be alerted of outbreaks for them to investigate. In turn, they should then inform the health authorities of the appearance of unusual viruses or epidemics elsewhere in the world and of the appropriate technical measures which should be taken.

The 1960s witnessed a rapid expansion of the global network of influenza laboratories. By 1969 there were two international centers and 80 recognized national influenza laboratories in 55 countries. National centers are designated by national authorities and are recognized by WHO on the basis of technical ability, and willingness to send freshly isolated strains and virological and epidemiological information to one of the WHO collaborating centers for influenza reference and research [34]. By 1979 the number of national centers had grown to 101, located in 72 countries [35]. Today, there are 110 national centers in 82 countries, and four WHO Collaborating Centers for Influenza Reference and Research: Centers for Disease Control and Prevention, Atlanta (USA); National Institute for Medical Research, London (UK); WHO Collaborating Center for Influenza Reference and Research, Melbourne (Australia); and the National Institute for Infectious Diseases, Tokyo (Japan). Researchers at these centers must constantly detect the major new influenza viruses.

With respect to pandemic surveillance, the primary goals of the WHO global programme have remained constant over the last half century. They are: to gain an understanding of the epidemiology of influenza and to promptly isolate influenza viruses from new outbreaks and distribute them for vaccine production [16]. This responsibility is executed in close cooperation with the network of national and international laboratories that has been put in place over the last half century.

This network helps WHO to monitor influenza activity all over the world and provides the network with the viral isolates and information it requires to decide which new variants will be used to produce influenza vaccines during the following season. Each year, information about the viral strains isolated over the previous 12 months is analyzed and used to determine the composition of the influenza vaccine to be administered during the coming influenza season. WHO is currently strengthening its network of national centers by encouraging governments to make available the resources needed to facilitate the exchange of information and reagents between centers, increase the number of centers in developing countries and ensure that all centers are linked electronically and in regular contact. The information supplied by this network enables the organization to regularly update WHO's WWW site (FluNet) and to publish the information in the Weekly Epidemiological Record, which report on the global disease situation.

In case of a pandemic, the WHO Task Force, may decide, in collaboration with the National Influenza Centers and the WHO Collaborating Centers, to:

- issue a pre-alert to vaccine manufactures and provide a potential vaccine strain,
- request the collaborating centers to start producing and distributing reagents,
- request the national influenza centers to heighten surveillance,
- provide logistic support to the national laboratories to ensure quick and safe shipment of isolates to the collaborating centers,
- alert national authorities to check, and if necessary update, their pandemic plans,
- ensure rapid and free exchange of information.

3.4. Influenza—a "riddle wrapped in mystery inside an enigma"

> If influenza is a riddle wrapped in mystery inside an enigma, then the viral genes are the riddle, the variable surface antigens for which they code are the mystery, and the course and cause of epidemics the ultimate enigma [42].

Considerable progress and understanding has been achieved by more than a half-century of research on the "riddle, mystery and enigma" of influenza. Initially conducted by a hand-full of national laboratories, this effort has evolved into a truly global effort with laboratories from all over the world participating. However, despite the accomplishments to date, much more is needed. Scientists need methods to determine, early in their existence, which emerging viruses pose the greatest threat to human beings. Additional subjects for future research and development are the development of viable methods to interfere with their spread, and to protect high-risk communities from disease. Also of vital importance is the need to develop methods for vaccine production that will allow for a more rapid scale-up to meet urgent unexpected needs.

Public and political awareness of the ever-present potential of a worldwide pandemic needs to be strengthened. Despite this century's pandemics, influenza remains a poorly understood and appreciated infection. Headlines announce coming epidemics, the public is advised to seek vaccination, deaths are reported, especially when the numbers are unusually high, and then the influenza season is over. Even the recent outbreak of "chicken flu", which led to 18 human cases in Hong Kong, only claimed the public's attention for a few weeks.

Surveillance of influenza is made more difficult by existing gaps in the early warning system. A network is only as strong as its individual parts. Not only are there many developing countries not able to provide any early warning of an influenza outbreak, 25% of the 110 listed centers are inactive, that is, are not fulfilling the functions prescribed. Global surveillance is the key to early warning as well as to improved understanding of the epidemiology of influenza. But funding remains low and consequently there are few people to carry out the work. Field virologists will soon be in critically short supply, and the number of well-staffed and thoroughly equipped field laboratories in the third world is decreasing [43].

While surveillance in China has significantly improved in recent years, there are still areas in China that do not have sufficient surveillance. Furthermore, there are countries, which have high populations, have increasing trade with China, but do not have national centers. The global network must not concentrate only on China and nearby countries. A new pandemic virus could arise in any location where humans are in close contact with birds or animals that carry the virus. The live-poultry markets in the USA have already been noted as a potential source of a future outbreak. More elaborate agricultural systems, involving fish and other animals, are being developed rapidly in various parts of the world, with one likely consequence being the creation of new human health hazards and increasing number of outbreaks in areas where there is little or no active surveillance [44]. One such instance was the outbreak of influenza-like illness in a remote region of Papua New Guinea. Although no laboratory confirmation of influenza could be made, the outbreak was consistent with influenza and it was in a region where the domestic pig plays an important role in village agriculture [16].

Influenza is the oldest emerging virus that is still emerging [43]. It is one of a handful of old and new viral diseases that pose worldwide threats. The great pandemic of 1889–1890 took two months to move from Siberia to western Europe. Infected railroad passengers brought the pandemic virus from St. Petersburg to Warsaw and Berlin; other routes were the highways and watercourses. The pandemic established itself in North America during the same month it had reached western Europe, owing to the speed and volume of transatlantic shipping. Latin America and Africa were reached the following month, although it still took several more months for the virus to penetrate these large continents [11]. Today the same voyage could be made in a few days. Tomorrow, not only will the connecting times be even less, many more people will travel and will spread influenza from one side of the world to the other. The diminishing "size" of the world means that we must not miss any outbreak of what might become the next influenza pandemic. Influenza's link with decaying and eroding living conditions, including the natural environment, makes it imperative that that the poorest areas of the world have adequate surveillance and early warning coverage.

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